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Medical innovation and national experimental pluralism: Insights from clinical stem cell research and applications in China

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Abstract

The article focuses on the integration process of clinical stem cell research in China in the international arena of high-profile science. This development is analyzed against the background of a well-established landscape of informal and frequently for-profit forms of clinical experimentation with stem cells. In doing so, I trace the institutionalization of experimental clinical stem cell research and applications in China, its stepwise problematization, and metamorphosis into an object of regulatory concern and intervention. It will become clear that the transition toward adoption of an internationally recognized standard system in the clinical stem cell field is a complex and highly contested process. The long-standing absence of a coherent state-centered regulatory approach for clinical stem cell research and applications in China, has not only given rise to the realization of new economic opportunities, but also to a multi-stranded innovation culture, which is characterized by knowledge exchanges and collaborations between highly diverging socio-technical and epistemic communities. I will make sense of these processes through the concept of "national experimental pluralism".

Keywords: clinical stem cell research; translational research; evidence based medicine; scientific standards; science regulation; China

Introduction

Clinical research for new drugs and medical technologies in China has in recent years been marked by the striving toward independent innovation and the strengthening of domestic research, testing and production infrastructures (Ding *et al*., 2011). This trend has been accompanied by the adoption of international scientific and ethical clinical research standards, promulgated in regulations for the administration of

clinical trials, their ethical review, and mandatory certification of research hospitals according to Good Clinical Practice (GCP) guidelines (CURE, 2009; Li, 2011). International standards also manifest in closer adherence to evidence-based medicine (EBM) protocols for the evaluation of new medicines, observed by the Chinese State Food and Drug Administration (SFDA), especially since its reform in 2007 (Li *et al*, 2008). The propagation of international standard regimens initially focused particularly on the development of conventional drug products, but was extended more recently to evaluation procedures in Traditional Chinese Medicine (Tang *et al*, 2008), for gene therapies (Peng *et al*, 2008), and other advanced medical technologies (Qiu, 2009).

In contrast, clinical stem cell research and applications, focused on in this article, have only lately become the object of regulatory attention in China. A first attempt, within the context of a regulation for novel medical technologies, was introduced in 2009 (Cyranoski, 2009). However, this attempt was never completed and a new and more comprehensive regulatory approach has been in preparation since 2008. The Chinese Ministry of Health (MOH) has issued a first phase of this evolving regulatory framework in January 2012 (MOH, 2012). Harmonization with the international system, however, has with this initial step not yet been realized.

In this article, I delineate the institutionalization of experimental clinical stem cell research and applications in China since the early 2000s. I show a stepwise problematization of the field of stem cell research and its metamorphosis into an object of regulatory concern and intervention. In part one, I provide an overview of the diverging modalities of stem cell-based clinical experimentation in China, and introduce the actor groups that push for the adoption of internationally recognized research standards and regulatory protocols. In part two, I focus on the problematization and emerging regulatory situation of the clinical stem cell field in China. Then, in part three, I show that the long-lasting absence of a coherent state-centered regulatory approach for clinical stem cell research and applications in China, has given rise to a multi-stranded innovation culture, which is characterized by knowledge exchanges and collaborations between highly diverging socio-technical and epistemic communities. I analyze these processes through the concepts of "national experimental pluralism".

The article is based on eight months fieldwork in China and Hong Kong conducted between July 2009 and April 2011. Eighty-two interviews were carried out

with stem cell researchers, staff of biotech companies, bioethicists, policy makers and patients. The article draws, furthermore, on observations of scientific conferences, expert meetings, visits to hospitals and research centers, and on documentary research, that included the analysis of policy documents, scientific journals, newspapers, websites and television programs.

Experimental stem cell research and applications in China

Experimental interventions using stem, or stem cell-like, cells have been carried out in China for more than ten years (Song, 2010). Enabled by the long-standing absence of state regulation for this new research field, a broad range of experimental approaches using stem cells has emerged during this period. These interventions range from cases of obvious fraud (BBC, 2009), through to highly formalized SFDA-approved clinical trials. The overwhelming bulk of experimental implantations of stem cells in China, however, fall in between these two poles. They are carried out as (1) patient-driven experimental treatments, (2) profit-driven experimental therapies, and (3) research-driven observational or clinical pilot studies. A fourth group is comprised of the highly systematized phases I and II (soon III) clinical trials that have intermittently been approved by the SFDA since 2004 (Liao and Zhao, 2008). While the forms of clinical experimentation with stem cells in China do often diverge from international standard regimens, a slow but steady move toward the adoption of internationally recognized clinical research protocols is evident in recent years.

Significantly, this transition process has not primarily been propelled by the state, but by the agency of a select group of Chinese high-profile researchers and their international research partners. These groups have worked continuously to transform and standardize local research infrastructures and to harmonize conceptions of clinical research methodology and ethics with international standards. These efforts have taken place through capacity building and scientific self-governance efforts in the context of concrete clinical projects and beyond the level of state agency (Rosemann, 2012). The MOH, the government unit responsible for clinical stem cell research, has for many years been hesitant in its approach to the governance of clinical SC research and applications in China.[1] The MOH has, however, facilitated the adoption of

[1] Note: While basic stem cell research falls under the joint responsibility of the Ministries of Health and Science and Technology (see Salter and Qiu,2009), clinical research and applications falls solely under the responsibility of the MOH.

international standards in the stem cell field indirectly, by promoting EBM in medical education (Li *et al*, 2008), by imposing stringent regulations for drug evaluation procedures by the SFDA, and by demanding GCP certification for research hospitals (Li, 2011). Furthermore, as will be shown in part two, the MOH is currently in the process of issuing a comprehensive regulatory approach for clinical stem cell research and applications. This step will undoubtedly propel and formalize the transition toward the adoption of international standards further. Before commenting on these issues in greater detail, however, I provide a brief overview of the four central modalities of experimental clinical intervention with stem cells that can be observed in China today: patient-driven, profit-driven and science-driven forms of clinical experimentation.

Patient- versus profit-driven experimental interventions with stem cells

Patient-driven forms of clinical SC applications are experimental clinical interventions in which doctors test an unproven treatment. These typically involve a seriously ill patient whose life expectancy is low and for whom all existing treatment options have failed. With informed consent, such experimental intervention is allowed in paragraph 35 of the Declaration of Helsinki (DoH, 2008), and practiced in many countries in the world. Numerous such interventions have been carried out in China, with some having been reported in medical journals (Gu *et al*, 2003; Zhu, 2006) and shown repeatedly on state television (see for example, CCTV, 2007, 2010). Such patient-driven forms of experimental treatments are commonly provided by doctors in first-tier hospitals, and are not usually linked to commercial interests. As the head of a clinical research institute in a large hospital in Beijing pointed out, fees may be charged, but these are restricted to operating expenses for hospital beds, material and equipment. Costs for patients or their families do not involve the salary for hospitals or doctors. Experimental treatments are commonly provided to patients of a clinical specialist, who tests a newly developed treatment approach, on a small number of his or her most seriously ill patients. Sometimes, particularly if conducted in first-tier hospitals, the results of these clinical experiments are recorded and presented at medical conferences, and occasionally published in peer-reviewed medical journals (Peng *et al*., 2005; Li *et al*, 2007).

Profit-driven experimental therapies, on the other hand, follow a different pattern. The provision of potential help to patients in need is here part of a logic of

commercial calculation, and the object of strategic investment. A novel type of economy has thus emerged based on new sets of relationships between clinical service providers, scientists, local investors, government officials and patients. Services are usually offered to a very broad patient clientele with different disease types and at various disease stages. For example, some companies apply one or two experimental methods to more than 70 different disease conditions.[2] Experimental for-profit treatments are generally provided in private hospitals, military hospitals or in privatized units of first and second-tier public hospitals, which are often especially designed for the purpose of stem cell therapy (Qiu, 2009; Song, 2011). Providers of commercial experimental stem cell therapies, as stated by the sales manager of a large healthcare equipment supply company, do only in few cases engage in more systematic and long-term collection of clinical data, and commonly eschew peer-reviewed publications, so as to hide technological details, to cover up negative data, flaws or adverse effects.

Occasionally, however, the boundaries between patient- and profit-driven forms of experimental treatments are blurring. Therapeutic procedures that have been applied as non-profit first-in-human experiments are then rapidly provided as for-profit experimental therapies. An example is the General Hospital of Armed Police Forces in Beijing. After some animal studies and initial experiments in patients with neural stem cells in 2003, the hospital converted its services to for-profit. In 2011 it had conducted 2847 treatment episodes.[3] What happens in such cases, is the on-the-spot routinization of a non-systematically proven experimental treatment approach where some degree of efficacy, and no apparent adverse effects, can be observed. This rapid move from non-profit to for-profit is enabled by the fact that controls for experimental treatments with stem cells in China currently lie exclusively in the hands of hospital IRBs, without any forms of external supervision (CURE, 2009). Furthermore, the shift is facilitated because patients expect to pay for experimental treatments in the strongly commercialized health-care system of China. This has been pointed out in interviews with both, clinicians and patients. Consequently, some of these clinical service providers make substantial amounts of money. Beike Company, for instance, which has treated more than 9000 patients, has reportedly generated one

[2] See the list with "treatable diseases" on the website of Beike Biotech: http://stemcelltreatmentnow.com/index.php/treatment/treatable-diseases.html
[3] http://www.neuralstemcell.com.cn/ksjj/

hundred million US dollars until 2010 alone (Sipp, 2012). An estimate in the journal *Nature* states that there were between 100-150 for-profit stem cell clinics in China in 2009, but the actual number is uncertain (Cyranoski, 2009).

Research-driven experimentations with stem cells

A broad range of research-driven clinical stem cell applications is going on in China. These experiments gather structured forms of evidence, but their protocols do not conform fully to international scientific requirements set out by other drug regulatory authorities or top international journals. At the less systematic end, in terms of research methodology, one finds open-label observational studies, some of which contain cross-sectional elements that compare the results from different types of treatment intervention. For example, the gastroenterology department of a first-tier military hospital in Central-South China, started to test an autologous stem cell treatment in 2009 and later a treatment based on mesenchymal stem cells (MSC) in patients with acute liver failure. A high risk of rapid mortality, together with high costs and long waiting times for liver transplantation, form severe challenges to these patients in China (Wang, 2009). These conditions, and the apparent success of the experimental treatment in a first patient, justified more interventions and, prior to September 2010, more than 130 experimental treatment episodes had been provided (Chen, 2010). As reported by the PI of this study at a stem cell conference in China in 2010, systematic records of the treatment results were taken of all patients along some standardized outcome measures (*ibid*.). A colleague of this researcher commented, however, that the design and results of such observational treatment series are far from systematic enough to be accepted by a good journal. In his view, though, these data provide important precursory information on the efficacy and safety of specific treatment pathways, which then can be tested in systematic clinical trials later.

In addition to such semi-systematized observational studies, however, a larger number of more systematically designed clinical studies have been carried out in China. These studies qualify either as clinical pilot studies or as randomized clinical trials, of which only very few involve control groups (see for example Wang *et al*, 2007). Liao and Zhao, in a review of 18 publications of clinical stem cell research in China, concluded in 2008 that, even though important progress in the field has been made, some of the trials were not done well. In certain hospitals, for instance, cells were used that were not well characterized (2008, p. 613). They argue that without

mandatory SFDA approval of stem cell clinical trials, data on the safety and efficacy of these studies cannot be guaranteed (*ibid.*).

The Move toward International Integration

What can be observed in the clinical stem cell field in China today is a slow but steady move toward the adoption of internationally recognized standard protocols. Two parties in particular propel this transition. The first is a small group of high-profile researchers in China who aim to develop SFDA-approved stem cell-based medicinal products, which can be formally marketed in China, and reported in top international journals. The second is investigator-initiated international clinical trial partnerships that are preparing multi-centered clinical trials in China and other countries. Necessarily, these must accord with international approval and review protocols in order to produce credible data.

Clinical stem cell researchers in China, who seek SFDA-approved clinical trials in the context of an investigational new drug (IND) procedure, are currently a rather small group. These persons have usually obtained training or professional experience abroad, and have a dual educational background as both research scientists and medical doctors. These researchers do mostly oppose the uncontrolled experimental research landscape with stem cells in China, and call for far-reaching regulatory controls. According to a high-ranked researcher from a renowned military hospital in Beijing, for instance, China should use the same approval and review protocols as handled in the United States, if it comes to stem cell-based clinical trials. From the viewpoint of this researcher, the diluting of internationally recognized standards, by adjusting them to specific conditions found in China, will result in isolation, and pre-empt possibilities for publications in international journals and high-level international collaborations. It will pre-empt, furthermore, the development of stem cell-based medicinal products or technologies in China that can be internationally licensed and marketized. This view corresponds to the approval protocols for efficiency and safety of drugs and pharmaceuticals that are currently used by the SFDA, which follows procedures set out by the US Food and Drug Administration (FDA) (RJS, 2010).[4]

[4] http://www.sfdachina.com/info/50-1.htm

However, such harmonization has not yet occurred in the clinical stem cell field. In fact, review and approval protocols for IND applications of stem cell products have not yet been publicly issued by the SFDA. Because comprehensive evaluation directives for the licensing of stem cell therapeutic products are still in a process of negotiation, the SFDA appears to have taken an extremely careful stance in recent years. According to a stem cell researcher who acts as external advisor to the SFDA, the agency approves the step from preclinical to clinical studies currently only for stem cell products that have previously obtained approval by a drug regulatory agency in the United States or Europe. Numerous researchers I talked to expressed severe complaints in this respect. This situation was widely assessed as slowing down clinical innovation processes in China, as preventing international integration and recognition, and as increased the number of clinical trials carried out exterior to review by a drug regulatory agency.

A related issue is that SFDA responsibilities are limited to the review of clinical trials with standardized stem cell-based medicinal (batch) products. Most therapeutic approaches with stem cells in China, however, are based on the transplantation of cells from *one-donor-to-one-patient*. These are categorized in China as medical technology, and not as medicinal products. Accordingly, they fall out of the jurisdiction of the SFDA.

Until January 2012, however, clinical trials with stem cell-based medical technologies had to be subject exclusively to hospital intern IRB review. While this situation has amplified possibilities for clinical experimentations, it has simultaneously deprived several researchers of the chance to obtain approval and feedback by a national-level drug regulatory authority. According to the founder of a stem cell R&D company in Northern China, this has in many institutes prevented a boost in research quality, and has increased safety risks for partaking patients.

International clinical research collaborations are another important vector in China, which pushes segments of the stem cell field toward the adoption of international standard protocols. Such projects are commonly committed to rigorous EBM standards, and are required to seek approval and review procedures of drug regulatory authorities in several countries simultaneously. To my knowledge, there is presently only one large-scale international partner project active in the clinical stem cell field in Mainland China, the China Spinal Cord Injury (SCI) Network. The China SCI Network is an evolving multi-center clinical trials infrastructure that aims to test

stem cell-based therapeutic approaches for SCI. It brings together researchers and hospitals across Mainland China, Hong Kong, Taiwan and the United States.[5] In a long-term capacity-building project, the network has since 2006 carried out intensive training and educational programs, to enable standardization of research design, ethics protocols, quality assurance measures, cell transplantation methods and GCP requirements (Rosemann, 2012). As members of the network emphasized in interviews, these criteria must be met, to satisfy the requirements of the drug regulatory authorities from the four regions, as well as to create compliance with publication criteria of top international journals.

While international clinical research collaborations such as the China SCI Network facilitate the integration of the clinical stem cell field in China into the international arena, they are not yet very popular. The reasons for this include: the unclear regulatory situation for clinical stem cell research in China, language barriers, and the enormous time and money-intensive process of building up a cross-continental multi-sited clinical infrastructure that produces reliable and standardized data. However, due to the relatively low labor costs in China, the availability of good clinical facilities and CRO services, the high numbers of available patients, and the market potential in China, there is a huge interest among both academic investigators and biotech companies to get collaborations going in China. A range of seed partnerships indicate that the formation of clinical innovation through international clinical trial partnerships will, in the coming years, play an important role in the stem cell field in China.[6] If this happens, these alliances will play a crucial role in the transition to the widespread adoption of systematic science-driven forms of experimental clinical research with stem cells in China.

Problematization and regulation

I turn now to the contrasting forms in which clinical research and applications with stem cells have emerged as problems in China, and to the conceptions of ethics and research governance that underlie these positions. I then analyze the ways in which these local forms of problematization have informed the evolving regulation for clinical experimentation with stem cells in China, and show how this emerging regulatory approach relates to international standard regimes for clinical stem cell

[5] See: http://www.chinascinet.org/
[6] See BioTimes Asia: (http://biotimeasia.com/)

research. The ethics to which I refer here concerns the diverging logics, interests and experiences which emerge at the interface of technology research, politics and culture (Ong, 2010, p.13). Articulations of ethics can evolve at different levels and scales (that is, patients, professional groups, states, companies, religious collectivities, etcetera), and reflect tensions between the priorities and worldviews of specific stakeholders or social groups. They are, furthermore, closely bound to issues of power and representation (Sleeboom-Faulkner, 2010). Regulation, in contrast, refers here to the efforts of states to shape the governance of technology research in relation to public interests (Van Zwanenberg *et al*, 2011, p. 12).

In regulatory debates on clinical stem cell research in China, a tension can be observed between forms of ethical reasoning that prioritize the stringent protection of human experimental subjects, and opinions that emphasize the value of rapid scientific progress for economic and social development. In the latter register, we see a climate of high expectations and hope that has been initiated by the media, scientists, clinical service providers, as well as politicized innovation and development discourse. The first experimental treatments with stem- or stem cell-like cells in the early 2000s, for example, were by the media celebrated as important breakthrough advancements (Liu and Xing, 2002; CCTV, 2002), and as indicators of China's rapid scientific progress (CCTV, 2003). Supportive coverage on experimental stem cell therapies on China's state television has continued over the years, with treatment episodes framed as indicators of scientific development and hope for patients (CCTV, 2003, 2007, 2010). Positive associations with experimental for-profit stem cell therapies in China have been reinforced furthermore, through high profile advertising campaigns launched by stem cell clinics, who use photos of high-ranked politicians posing with clinical service providers, and a political discourse that highlights rapid and independent innovation and technology-driven economic development (Song, 2011; Sipp, 2012). Risks for patients and doubts regarding the efficacy of experimental stem cell therapies are commonly downplayed in such representations.

Notwithstanding these campaigns, the safety, feasibility and profit-driven character of these treatments have in recent years been the subject of critical commentary and debate in various print media. The news magazine *New People's Weekly*, for example, launched a front page story in 2007 titled: 'A Truth Inquiry of Stem Cells: "Gambling" on the Hospital Bed', which cast serious doubts on both the

safety and efficacy of experimental stem cell treatments. The article asks for greater standardization and specification of clear application norms (Huang, 2007). Calls for systematized forms of evidencing were also demanded by the influential news magazine *Southern Weekend*, which asked whether an initially highly praised experimental treatment for SCI is a "science bubble" rather than a "striking breakthrough". The article concludes with a plea for more controlled randomized clinical trials in China (*Southern Weekend*, 2006). Furthermore, calls for reliable regulation have come from high-profile, Chinese researchers (Liao and Zhao, 2008), as well from scientists and commentators from abroad (Cyranoski, 2009, 2012; ISSCR, 2008; Hyun, 2010).

The MOH, which is the government unit responsible for the regulation of clinical research and applications in China, has reacted to these demands in three ways. First, in 2007, it decided to regulate experimental for-profit stem cell therapies in the context of a regulation for new medical technologies, which was launched in 2009 (Chen, 2009). Second, in 2008, it assigned an expert committee in Shanghai to develop a draft regulation for the entire field of clinical stem cell research (Qiu *et al*, 2010). A draft was submitted to the MOH in 2010, and is now in a phase of internal finalization. Third, a notification by the MOH has been issued in January 2012, which has introduced a phase of evaluation and preliminary rectification.

The 2009 regulation and its impact

On 1 May 2009 the MOH promulgated the 'Management Measures for the Clinical Use of Medical Technologies', a regulation that classified a range of new medical technologies and procedures into three categories. Stem cell transplant technology was grouped into category III, which included technologies considered as risky, ethically controversial and in need of clinical verification (Qiu, 2009). To implement the regulation the MOH assigned five institutions (Chen, 2009, p. 271), among them the Chinese Medical Association, the Chinese Hospital Association and the Chinese Doctors Association. According to an associate of the MOH in Beijing, clinics that used stem cell transplantation technology were summoned to register at these institutions. These organizations in turn were assigned to grant licenses on the basis of newly formed assessment criteria and review and inspection committees. In practice, this regulation has not yet been implemented for stem cell transplantation technologies. As stated by a senior stem cell scientist, who as a member of the

Chinese Doctors Association was involved in the formulation of review criteria, there were widespread disagreements among experts of the assigned five institutions, over the precise characteristics of these criteria, over feasible implementation pathways, as well as the extent to which the situation should be controlled.

It is noteworthy that the 2009 regulation, despite its non-implementation, has impacted the clinical stem cell field in China in several ways. According to a clinical researcher from the People's Hospital in Beijing, for example, the hospital issued a ban on all forms of (non-SFDA approved) experimental stem cell research and clinical trials, until reliable regulatory structures are in place. Similar decisions can be reported from other first-tier hospitals. Clinical researchers from three renowned state hospitals told me their departments had halted clinical experimentations with stem- or stem cell-like cells after 1 May 2009. One reason for this was fear of legal prosecution, since none of the hospitals was yet able to receive an official license for the use of clinical stem cell technology, as demanded in the MOH regulation.

The delimiting impact of this regulation has been much lower, however, in private and lower-ranked state and military hospitals. According to a Chinese marketing manager of a multi-national supply firm for laboratory equipment, for instance, a market evaluation revealed that the purchase of CO_2 incubators for the culturing of mammalian cells had increased in the third and fourth quarter of 2009 by more than 50 percent. Allegedly, virtually all orders in that period were issued by private hospitals functioning as cell therapy centers. According to this marketing specialist, the increase in CO_2 incubator purchases to commercial providers of stem cell therapies is explained by the fact, that the 2009 regulation addressed stem cell technology only in a very minimalist way; without any specification of review criteria and implementation pathways. To commercial providers of cell therapies this move signaled that stringent controls for experimental stem cell therapies were unlikely to be carried out in the near future. In the light of a growing demand for these therapies, these providers decided upon investment and market expansion.

The emergence of a comprehensive regulation

In 2008 the Science and Education unit of the MOH authorized an expert committee of medical ethics chaired by Prof Chingli Hu, to develop a comprehensive draft regulation for clinical research and applications with human stem cell in China. After a two-year consultation and preparation process, a draft was submitted to the MOH in

October 2010. This proposal has subsequently been under internal consideration, and is expected to form the foundation of a finalized version that is expected soon.[7]

A central premise of this draft is the promotion of standardized and rigorous scientific forms of clinical stem cell research (Hu *et al*, 2010, p.27). It asks for methodical preclinical studies and the generation of reliable safety data, as well as standardized clinical trials that precede clinical applications (p.27). These trials shall be subject to approval and review procedures under the MOH and the SFDA (which since 2008 has been a subunit of the MOH). Only qualified and licensed hospitals would be able to provide approved clinical applications (p.37). Furthermore, the draft stipulates that the quality and safety of used cells must be subjected to reliable controls and documentation (p.32). Medical institutions that violate these principles will be forced to stop stem cell-based clinical trials or applications for a period of five years (p.37).

The draft specifies approval and review procedures for three central forms of clinical research and applications with stem cells. First is approval of clinical trials and applications of *stem cell based drug products*, that is, standardized batch products based on amplification of cells from one or multiple donors. Responsibilities for evaluation and market approval of these 'off-the-shelf' stem cell products (commonly regarded as the most risky treatment form with stem cell) shall be handled by the SFDA, and be based on systematic preclinical studies and closely reviewed Phase I-III clinical trials (p.36).

Second is approval of clinical trials and applications of *modified stem cells from a single donor to single recipient*. With reference to the 2009 regulation these treatment forms were defined as medical technology. Regulatory distinctions are made in this respect between autologous/allogeneic stem cells, and minimally/extensively manipulated stem cells. Approval of minimally processed autologous stem cells, which is seen as the least risky group of cells, shall occur through the MOH Bureau of Medical Administration. More extensively manipulated cells, particularly from allogeneic sources, shall be approved by the MOH Bureau of Science and Education. Application and review procedures shall be handled by the 31 province-level sub-branches of the MOH, with the MOH in Beijing as the central supervising agency. Third is approval of *experimental therapeutic approaches with*

[7] This information is based on a presentation of this draft regulation, generously provided by Prof Chingli Hu and his team in Shanghai, on 21 January, 2011.

stem cells. Experimental for-profit applications shall be strictly delimited. In accordance with article 35 of the Helsinki Declaration first-in-human experimental treatments with stem cells shall be allowed, but in a low number of patients, and according to clear approval criteria. Applications and oversight shall occur through specialized ethics committees, at the provincial MOH branches.

With this draft regulation, a clear step toward international harmonization has been set into motion. In regulating medical procedures with stem cells proportionate to risk, for example, the Chinese draft regulation follows essentially the approach that is also taken in the EU (Faulkner 2009, p. 641). Differences exist, however, with respect to terminology and the allocation of responsibilities. In the EU, all experimental medical procedures with stem cell (including autologous stem cell for non-homologous use) have since 2007 been classified as *advanced therapy medicinal products*. These are regulated under the centralized auspice of the European Medicines Agency (EMA) (*ibid*. 2009; EMA, 2012). The 2010 draft regulation for China, on the other hand, follows a slightly different strategy. For one thing, approval procedures are divided between the categories 'medical products' and 'medical technologies. For the other thing, responsibilities are not done by a centralized drug regulatory agency, but split across three administrative units of the MOH, each with its own subsidiary branch organizations at a provincial level. Since the draft regulation is still likely to undergo significant revisions, it is too early to say what the implications of these differences for processes of regulatory harmonization and international collaborations will be. Further research into these directions, together with a focus on local implementation, will be of interest.

The January 2012 notification

On 6 January 2012, the MOH issued a regulatory document called 'Notification on Self-Evaluation and Self-Correction Work regarding the Development of Clinical Stem Cell Clinical Research and Applications'.[8] With this document an initial one-year phase of a more comprehensive regulatory approach has been initiated, whose precise details have not yet been publicized. In the January 2012 document, four subsequent stages of this forthcoming approach have been announced: self-evaluation

[8] http://www.moh.gov.cn/publicfiles/business/htmlfiles/mohkjjys/s3582/201201/53890.htm

(*zicha*), self-correction (*zijiu*), re-certification (*chongxin renzheng*) and standardized management (*guifan guanli*).

The initial one-year phase that is set out in the 2012 document, however, addresses only the first two of these stages: self-evaluation and self-correction. Self-evaluation of the hospitals that carry out stem cell-based clinical research and applications shall occur in the following way. First, clinics are required to fill in the 'Self-Evaluation Form for Inquiry into Conditions of Stem Cell Clinical Research and Applications'.[9] In this form, clinics are asked to report truthfully on previously and currently developed kinds of clinical research and applications with stem cells. Information is requested on (1) types of cells and forms of cell-processing, (2) the disease types for which cells have been used, (3) forms of ethics and regulatory approval mechanisms, (4) informed consent procedures, (5) information on risks and experienced problems, (6) sources of funding and patient fees, (7) number of patients experimentally treated, and (8) publications or summarizing reports from clinical trials or other types of clinical studies. Second, this information is evaluated by province-level MOH workgroups, which are coordinated by the 'Stem Cell Clinical Research and Application Standardization and Rectification Work and Leadership Group', co-founded by the MOH and SFDA in Beijing (paragraph 2). The task of these province-level workgroups is to appraise the incoming data, to produce summarizing reports to Beijing (paragraph 4), and during later stages, to play an active role in the implementation and enforcement of the regulation (paragraph 2).

Self-correction means that all institutes that have not yet received approval, either by the MOH or the SFDA, must stop clinical stem cell research or application activities until approval has been obtained. Institutes that continue to carry out unauthorized clinical research or applications have been announced to be targeted as focal points for rectification (paragraph 2). On the other hand, clinical trials for stem cell products that have obtained approval by the SFDA are expected to act in strict accordance with the requirements set out by the SFDA, and in compliance with the Chinese GCP standards (paragraph 2). The document has announced that no registration applications will be accepted by the MOH or the SFDA until July 1 2012 (paragraph 2). Information on how applications for registration will be handled,

[9] This document has been put on the MOH website. http://61.49.18.65/publicfiles///business/cmsresources/mohkjjys/cmsrsdocument/doc13829.docx Translations of these two documents can be requested from the author of this article via e-mail.

however, has not been provided in the text. Uncertainty also remains as to how non-compliance will be dealt with, and which role the MOH and its province-level workgroups will play in this. It is not clear, furthermore, whether military hospitals (that operate under the command of the Health Department of the Army General Logistics Department), will be subjected to the same review and approval procedures as state hospitals, or whether a different regulatory approach shall apply.

National experimental pluralism

With the January 2012 notification, and the draft regulation of 2010, the ministry has signaled that it is committed to methodical preclinical studies, approval procedures based on systematic clinical trials, controls of cell processing and manufacturing, and to the penalization and shutting down of clinics that do not meet required standards. These issues reflect, by and large, the benchmarks set out in the 'Guidelines for the Clinical Translation of Stem Cells' of the International Society for Stem Cell Research (ISSCR, 2008), which formed a central reference point for the regulation prepared by the drafting committee led by Chingli Hu (Hu, 2010, pp. 23-4). If successfully implemented these steps will bring governance of the clinical stem cell field in China into line with the international standard system

In creating congruence with internationally recognized clinical standards in the stem cell field, the ministry is gradually establishing new boundaries of inclusion and exclusion. Many of the forms of clinical experimentation that have become institutionalized and widely sought after in recent years, will be delegitimized. However, this change in status may be some time off. Not only will technical standards and implementation pathways of the emerging regulatory framework have to be defined in detail, but there is also the challenge of developing adequate enforcement mechanisms. According to a *Nature* report in April 2012, not one clinic had signed up at the ministry in the required way, and many hospitals continued to offer treatments, despite the decree that clinical applications which have not yet received approval by the MOH or SFDA should not proceed (Cyranoski, 2012). Accordingly, until stringent enforcement procedures are in place, the landscape of clinical experimentations with stem cell in China will remain characterized by the coexistence of multiple and highly diverging forms of experimentality.

In this respect, a complex and multi-stranded clinical innovation culture has developed in the stem cell field in China. This culture is characterized by

collaborations and knowledge exchanges between highly contrasting socio-technical and epistemic communities. Let me explain this briefly through the concept of "national experimental pluralism". The term refers to the deployment of divergent modalities of experimental clinical application through different communities of practice, under a shared national jurisdiction. In the clinical stem cell field in China, as I have shown above, multiple forms of clinical experimentation exist side-by-side. These differ with regard to recruitment strategies, clinical methodologies and the discursive practices through which claims on efficacy, safety and ethical validation are created and justified. These disparate forms of experimental clinical intervention (and the goals, values and legitimization frameworks on which they are based) are situated in diverging socio-technical communities that have evolved under the permissive regulatory approach to clinical stem cell applications in China. I suggest that this pluralization of experimental practices and communities, has given rise to a clinical innovation culture that in many respects diverges from linear lab-to-clinic models of drug development, as drug regulatory authorities, such as the US FDA or the Chinese SFDA, promote them. Due to the long-standing absence of a regulatory framework for clinical stem cell research in China, a more dynamic and circular process of clinical innovation can be observed. Promising approaches with new cell types may be tested first in patients, then moved to the lab, and subsequently back to the clinic; either in form of (more) systematized pilot-studies or clinical trials, or as for-profit experimental therapies.

As Webster *et al* have pointed out in a recent article in *BioSocieties*, similarly pragmatic pathways of clinical translation can also be observed in the United States and Western Europe, in experimental clinical work with autologous stem cells (2011, p. 411). As the authors note, rapid translation from bench to clinical trials, with return feedback loops to the lab, before a phase of re-testing in the clinic, can be frequently observed in the development of autologous stem cell treatments (*ibid*, p. 411). In China, however, the situation is still different. For one thing, such circular patterns of clinical translation exist not only with autologous stem cells, but also with allogeneic cell sources, which are considered more risky. Furthermore, multi-directional knowledge transfers between bench and clinic in the stem cell field in China can occur across highly diversified institutions and actor groups, which employ starkly contrasting forms of data collection, ethical standards and approval procedures. This contrasts significantly with the situation in the United States or Western Europe,

where knowledge exchanges between labs, clinics, research institutes and companies unfold in a context of homogenized regulatory practices, unified technical and ethical standards, and a widespread commitment to systematic clinical trials.

An illustration of the opportunities that arise from the multi-directional knowledge flows between diverging sites and frameworks of experimentality in China is the use of allogeneic mesenchymal stem cells (MSC). Since 2004, MSC have experimentally been used in patients in China (Chen *et al*, 2004). These early studies, in combination with encouraging findings from abroad, have triggered a massive wave of basic, preclinical and clinical research with MSC (Liao and Zhao, 2008), as well as countless experimental for-profit applications. Research with MSC in China has resulted, moreover, in at least four standardized MSC-based medicinal drug products, which have applied for SFDA approval. Additionally, a large number of non-SFDA reviewed clinical trials and clinical trial-like studies with MSC have been conducted, for several disease conditions (Liao and Zhao, 2008; Han *et al*, 2011).

This coexistence of rapid clinical applications alongside systematic preclinical and basic research opens up possibilities that in the United Kingdom, for instance, would be unthinkable. For one thing, it has created opportunities for fast "tryout" trials, for example, the precursory testing of a new stem cell product in patients with different disease types, to identify the most promising uses for subsequent (and highly cost-intensive) IND application. For instance, in 2010 a senior researcher presented findings at an international conference. These finding were taken from clinical pilot studies for seven disorders in 153 patients, with a standardized MSC product developed in this researcher's lab. These studies were based on collaborations with local hospitals and aimed to create preliminary efficacy and safety data, on which basis to detect the most promising approaches for a planned SFDA application. Due to the absence of a regulation for stem cell-based clinical trials in the past, pilot-trials that precede IND applications at the SFDA have in fact been legal (provided IRB approval in involved hospitals has been obtained). Many researchers see such studies as a central element for clinical stem cell innovation in China because they allow for rapid and unproblematic evaluation of the clinical utility and feasibility of new products which can be tested more systematically later on. Many of the high-profile researchers with whom I spoke, nonetheless, reject such informal trials, and insist wholly on lab-to-clinic translations under review of the SFDA or MOH.

The coexistence of rapid clinical experimentations, often for-profit, alongside systematic preclinical studies and formalized clinical trials has created various other effects, which have benefitted the field of clinical stem cell research in China. Several researchers reported, for instance, that the high number of experimental treatments with MSC in patients with different diseases have delivered important preliminary insights regarding the treatment potential of these cells, and a rough estimate that MSC (after use in thousands of patients) are apparently comparably safe. According to Liao and Zhao, experimentations with MSC in clinical trials have also provided new questions for basic research in China (2008, p. 616). But feedback loops from clinic to lab occur also in the context of for-profit experimental treatments. Clinical service providers of for-profit MSC therapies, for instance, publish regularly together with basic scientists from key-state institutes and hospitals, in particular on mechanisms of functional recovery (Li *et al*, 2010; Tang *et al*, 2012). The market potential and widespread clinical applications with MSC in China have also intensified research on the sourcing, quality control and storage of MSC. AmCellGene Co. Ltd., for instance, a stem cell R&D company from Tianjin, has developed a standardized manufacturing procedure for the clinical use of umbilical cord derived MSC. This procedure encompasses cell collection, isolation, cryopreservation, characterization and administration, for the manufacturing of clinical grade MSC in the context of good manufacturing practice (GMP) compliant laboratories (Gong *et al*, 2012). Most important maybe, the large number of clinical applications with MSC has given rise to crucial hands-on experiences, in particular regarding cell transplantation and related surgical procedures, and to the availability of a clinical infrastructure, which can be used for systematic and multi-center clinical trials in the future.

Conclusions

In this article I have tracked the stepwise transformation of experimental clinical stem cell research and applications in China to an object of regulatory concern and intervention. It has become clear, that initial steps toward regulatory harmonization have been undertaken, but that more specific regulatory instruments will be required, if the process shall be completed. At present, the situation is characterized by what I have called “national experimental pluralism”, the coexistence of highly diversified

modalities of clinical experimentation under a shared national jurisdiction. I have suggested that the side-by-side of distinct experimental forms has given rise to a complex clinical innovation culture, which is characterized by multi-directional knowledge flows across starkly contrasting socio-technical and epistemic communities. This high level of experimental freedom, has become clear, has set into motion, novel economic and scientific opportunities. In the light of these new possibilities, incentives for regulatory harmonization have remained comparably low for many medical institutions. Stakeholders that promote the integration of the clinical stem cell research in China into the international arena are a relatively small group of high-profile researchers and R&D companies, as well as researchers that take part in international clinical research collaborations. The key incentives for these stakeholder groups are the development of formally approved medicinal stem cell products that can be accessed and marketed in multiple countries, and the opportunity to be published in top international journals. To achieve compliance with international clinical research and ethics protocols, these groups must rely on extensive forms of capacity building and scientific self-governance.

In contrast, providers of for-profit therapies and clinical researchers who do not seek international recognition, have little incentive to comply with international standard regimens. Many of the activities and economic undertakings of these groups would come under pressure through a shift toward consistent regulatory harmonization in China. At present, in any case, no regulatory mechanisms exist in China to enforce compliance with international standards in the clinical stem cell field. Even though, as shown in this article, oversight and approval mechanism are now endorsed by the state, there is a widespread consensus that regulatory controls should not be too stringent, so as not to inhibit scientific progress and delay public health and economic benefits.

Against this background, internal pressures for conformity with the international system can be expected to remain low. However, external forms of pressure for regulatory harmonization in the clinical stem cell field are currently also not very strong. In contrast to pharmaceutical drug research, in which international harmonization has been enforced by drug regulatory agencies and the pharmaceutical industry, the pressure is still low in regenerative stem cell medicine. A key reason for this, I suggest, is that the regenerative medicine field is still at an early development stage. Until now, the therapeutic potential of stem cell-based therapies has only in few

cases been demonstrated convincingly. Cross-border marketing of stem cell based products or procedures are still low, and it is mainly restricted to the informal sector. Investments from the pharmaceutical industry, moreover, have remained small. In the light of this situation, and the concrete forms of exchange and use value that the stem-cell-mode-of-production in China is already generating, the broad spectrum of experimental scientific and ethical practices to which this article has referred to, is well likely to persist.

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